

Postoperative recurrence in Crohn's disease - case presentation and review of the literature

Mihaela Dranga^{1,2}, Cristina Cijevschi Prelipcean², Otilia Gavrilescu^{1,2,*}, Alina Mihaela Moroşanu², Andreea Otea², Andrei Andronic², Cristina Aulinei², Catalina Mihai^{1,2}

1. „Grigore T Popa” University of Medicine and Pharmacy, Iaşi

2. Institute of Gastroenterology, „St Spiridon” Emergency Hospital, Iaşi, Romania

Abstract

Crohn's disease (CD) is an inflammatory bowel disease that can affect any segment of the gastrointestinal tract. Surgical therapy is reserved to those patients who does not respond to medical therapy. Surgery does not cure CD and the need for repeated surgery occurs in around 25% after 5 years and 35% after 10 years. These rates diminished in the last decades as a consequence of the use of earlier and more powerful therapies. We presented a case of a 37 years old male who presented with diffuse abdominal pain, bloating, 2-3 stools per day and a significant weight loss of approximately 10 kilograms in 6 months. The biological analyses were normal, but colonoscopy revealed a pseudopolypoid aspect with a stenosis at the right colon which did not allow the colonoscopy to continue. The patient was referred to surgery for occlusive syndrome. At 4 months postsurgery the patient has endoscopic recurrence and biological treatment with Adalimumab was beggined. After 1 year the patient was in clinical, biological and endoscopical remission, but after 2 years we notice endoscopic recurrence of the lesions. The treatment was intensified with no results and after that switched to Infliximab. After that for 6 years under this treatment the patient maintain remission. In conclusion there is a high risk of recurrence after surgery, but drugs such as metronidazole, azathioprine and biological therapy can reduce the rate of recurrence.

Keywords: Crohn's disease, surgery, postoperative recurrence, biological therapy

Introduction

Crohn's disease (CD) is an inflammatory bowel disease that can affect any segment of the gastrointestinal (GI) tract. Medical therapy is considered to be the treatment for most patients while operative management is reserved for individuals who fail medical treatment or develop potentially life-threatening complications. Between 70% and 90% of patients with CD will require surgery during their lifetime (1).

Case presentation

We present the case of a 37 years old male who presented in our clinic with diffuse abdominal pain, bloating, 2-3 stools per day and significant weight loss of approximately 10 kilograms in 6 months. He had no significant family history. He was nonsmoker and denies alcohol consumption.

He had past history of abdominal pain that goes along for 5 years. In this period he had multiple medical consultations and investigations: laboratory tests were normal - including celiac disease serology. A prior abdominal ultrasound and

an upper digestive endoscopy were normal. He was also investigated through a colonoscopy that showed no lesion, but it was incomplete, up to transverse colon. The diagnostics establish to the current admission were: Irritable bowel syndrome, Gastroduodenitis, Functional dyspepsia, Biliary dyskinesia, Lumbar pain for which the patient was treated with antispasmodics, gas absorbers, proton pump inhibitors (PPIs), prokinetics, probiotics, nonsteroidal anti-inflammatory drugs (NSAIDs) with no significant improvement. More than that the symptoms worsened in the last 3-4 months.

Corresponding author: Otilia Gavrilescu, Faculty of Medicine, "Grigore T. Popa" University of Medicine and Pharmacy, Iaşi, Romania; E-mail: otilianedelciuc@yahoo.com

Received June 17, 2020; **Accepted** September 14, 2020; **Published** October 20, 2020

Citation: Dranga Mihaela, Cijevschi Prelipcean Cristina, Gavrilescu Otilia, Moroşanu Alina Mihaela, Otea Andreea, Andronic A., Aulinei Cristina, Mihai Catalina. Postoperative recurrence in Crohn's disease - case presentation and review of the literature. Jurnalul de chirurgie [Journal of Surgery]. 2020; 16(4): 287 - 292

Copyright: © 2020 Dranga Mihaela et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

On the clinical examination we discover an underweight patient with tenderness in the right iliac fossa. The laboratory test were normal, except a lower MCV, HEM, and cholesterol. The coproparasitological examination and coproculture showed no sign of infections, and the toxins A and B for *Clostridium difficile* were

negative. We also perform an abdominal ultrasound that showed no modifications.

At the colonoscopy we found a pseudopolypoid aspect with a stenosis at the right colon which did not allow the colonoscopy to continue (Fig.1). The histopathological examination showed diffuse and follicular lymphocytic infiltrate, deformed crypts.



Fig 1. Pseudopolypoid aspect with stenosis in colonoscopy

We continue the investigations with a computed tomography (CT) that reveals excentric circumferential thickening with a maximum thickness of 10 mm, extended from the level of the last ileal loop to the level of the transverse colon, with an imprecisely delimited external contour and the infiltration of the adjacent fat. The CT also identified localized ileo-colic, peri cecal infracentimetric lymph nodes.

In evolution the patient develops occlusive phenomena so we refer him to the surgery where he has a right hemicolectomy, ileal resection (30 cm) with ileo-colic anastomosis.

The biopsy was pathognomonic for Crohn's disease: diffuse and follicular, transmural lymphocytic inflammatory infiltrate, which associates gigante -epiteloid granulomatous inflammation, without central necrosis. There are also 22 loco-regional lymph nodes

examined, 3 of them showing granulomatous inflammation with epithelioid cells.

The postoperative evolution was without complications and at 7 days the patient was asymptomatic with normal biological picture.

After surgery we started the treatment with Metronidazole 500 mgx2/day for one month and after that we added azathioprine 2 g/kg/day for 1 months. After a month the patient developed azathioprine side effects: abdominal pain, nausea, vomiting, increased pancreatic enzymes and we must stop the immunomodulator treatment.

At 4 months postoperative the patient was in clinical and biological remission, but in colonoscopy we discovered an inflamed mucosa at anastomosis with multiple ulcerations (Rutgers i3 activity score) (Fig. 2).



Fig. 2 Colonoscopy aspect before biological therapy

Postoperative recurrence in Crohn's disease

So after 6 months postoperative we started the treatment with biologic agents: Adalimumab in 160 mg/80 mg/40 mg and then 40 mg every 2 weeks with good clinical and biological outcome. The colonoscopy at 1 year

postoperative showed that the patient was in endoscopically remission (2-3 ulceration at anastomosis, normal mucosa – Rutgers score 1) (Fig. 3).

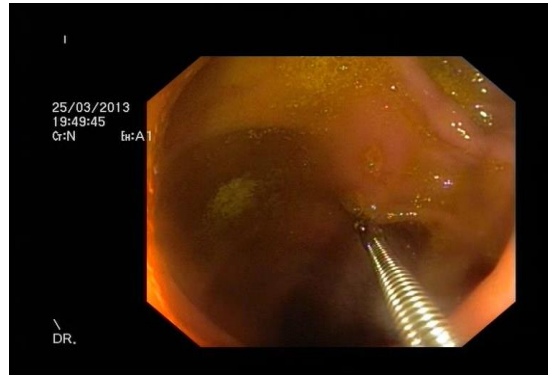


Fig 3. Colonoscopy aspect at 1 years post biological treatment

After 2 years postoperative, even though the clinical and biological remission was maintained, at colonoscopy we discovered endoscopic activity (multiple ulcerations, inflamed mucosa at anastomosis Rutgers score

3) so we intensified the treatment: Adalimumab 40 mg weekly.

After 3 months the patient was reexamined colonoscopically and the endoscopic aspect worsened (Fig 4).

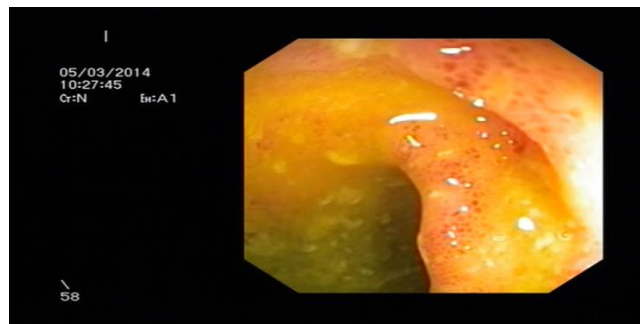


Fig 4. Colonoscopic aspect after intensification of biological therapy

We switch to Infliximab and after for 7 years the patient is in clinical, biological and endoscopically remission.

Discussions

The surgery does not cure CD. Certain risk factors contribute to the probability and severity of recurrence. About 70-90% of the patients will have endoscopic recurrence in the first year. Clinical recurrence rates amount to 20-37% after 1 year, 30% after 3 years, and 60% after 5 years depending on the patient population (2).

Typical symptoms of recurrence include diarrhea and abdominal pain, although various other differential diagnoses such as short bowel syndrome or irritable bowel syndrome have to be considered. The need for repeated surgery occurs in around 25% after 5 years and 35% after 10 years. These rates have diminished considerably in the last 1-2 decades, probably as a consequence of the use of earlier and more powerful therapies (3).

Several risk factors were associated with higher likelihood of CD recurrence. The presence of one or more of such risk factors should guide the postoperative follow-up. One of the most important risk factors is smoking. Therefore, all efforts have to be taken to convince patients to quit smoking. A shorter disease duration (< 2 years) at surgery also increases the risk for recurrence. Prior resections, fistulizing/penetrating disease as surgical indication, extensive bowel disease (> 50 cm), upper gastrointestinal involvement, male gender, granulomas in the resection specimen, histological inflammation at the ileal and possibly colonic margins are also relevant risk factors. Endoscopic recurrence usually precedes clinical symptoms. (4) For the assessment of endoscopic recurrence, the Rutgers's score was developed. So, the scores below i2 (i0, respectively i1) is consider endoscopic remission and the patients have 80% rate of no recurrence at 3 years. A score equal or above i2 is consider endoscopic activity. At i3 and i4 scores, 92% of the patients will have endoscopically severe disease at 3 years (5).

One of the study that compared different treatment options was a trial from 2013 conducted by Savarino. The study enrolled 51 patients with CD who had undergone ileocolonic resection who receive after 2 weeks from surgery ADA at the dose of 160/80/40 mg and then 40 mg every two weeks, azathioprine (AZA) at 2 mg/kg/day, or mesalamine at 3 g/day, and they were followed up for 2 years. The primary end point was the proportion of patients with endoscopic and clinical recurrence. The rate of endoscopic recurrence was significantly lower in ADA (6.3%) compared with the AZA (64.7%;) and mesalamine groups (83.3%). There also was a significantly lower proportion of patients in clinical recurrence in the ADA group (12.5%) compared with the AZA (64.7%) and mesalamine groups (50%) (6).

A recent meta-analysis from 2019 analyze 14 studies on patient with CD after intestinal resections. Most of the included studies compared the efficacy of anti-TNF agents to non-biological comparators (Azathioprine, 6-Mercaptopurine, Mesalamine or placebo) in preventing clinical, endoscopic, and histological postoperative recurrence. Based on the results, anti-TNF agents were significantly more effective in preventing clinical, endoscopic and histological postoperative recurrence (7).

Another problem that should be considered is which of the therapies is more effective: early treatment or endoscopically guided therapy. There are several studies that used early treatment with anti-TNF agents that showed very good result in preventing postoperative recurrence. In Yamamoto study, after 6 months of infliximab (IFX) the endoscopic recurrence was 38% (8). In Regueiro study after an years under the treatment with IFX the endoscopic recurrence was 58% (9). Similar result obtained both Mantzaris and Sorrentino using anti TNF agents (10,11).

In an study that took place in 2011 Bordeianou found similar clinical recurrence no matter what therapeutic strategy the authors have used (12).

On the other side the authors in the POCER study showed that endoscopically guided treatment in superior to standard treatment in obtaining smaller endoscopic recurrence rates (13).

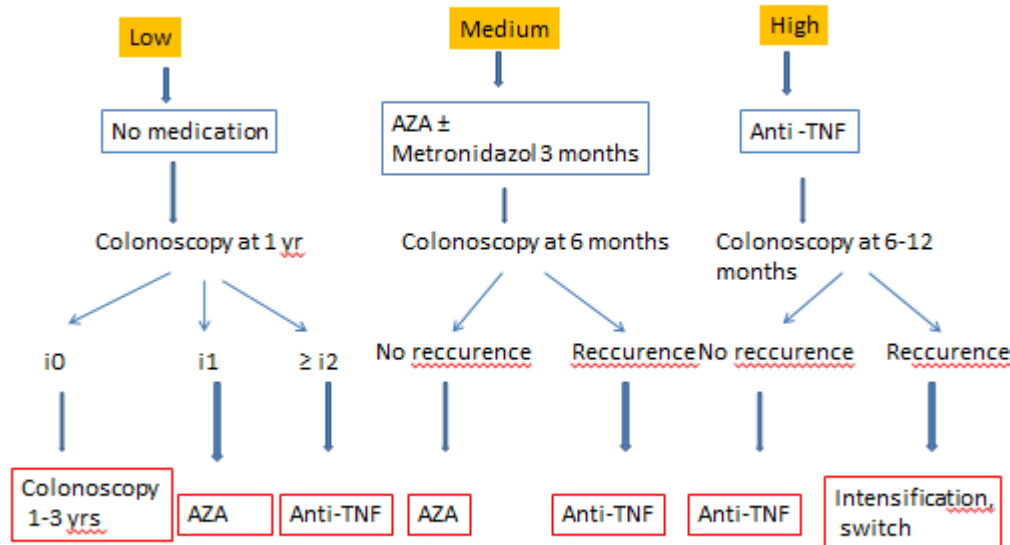
One of the study that used early therapy was the PREVENT study. The Prevent study evaluated the efficacy of infliximab in preventing postoperative recurrence of CD in 297 patients at 104 sites worldwide from November 2010 through May 2012. All study patients had undergone ileocolonic resection within 45 days before randomization. Patients were randomly assigned (1:1) to groups given infliximab (5mg/kg) or placebo every 8 weeks for 200 weeks. The placebo was considered any medication administrated prior to the patient except biologic agent (14).

The primary end point was clinical recurrence, defined as a CD Activity Index score >200 or a 70-point increase from baseline, and endoscopic recurrence (Rutgers's score i2) or development of a new or re-draining fistula or abscess, before or at week 76. A secondary efficacy end point was clinical recurrence before or at week 104. The authors showed that a significantly smaller proportion of patients in the infliximab group had endoscopic recurrence compared with the placebo group both at 76 week and in 104 week (30.6% vs 60.0% at 76 week and 22%vs 51.3% at week 104). Although a smaller proportion of patients in the infliximab group had a clinical recurrence compared with the placebo group, this difference was not statistically significant (12.9% vs 20.0%) (14).

A postoperative strategy of escalating treatment for endoscopic recurrence at 6 months was evaluated in the POCER (Post-Operative Crohn's Disease Endoscopic Recurrence) study. Patients were risk-stratified (high vs low) for CD recurrence than randomized to have an initial colonoscopy at 6 months or no colonoscopy until 18 months. All patients received 3 months of metronidazole, and high-risk patients were treated with postoperative thiopurine, or if they were intolerant, adalimumab. Patients undergoing a 6-month colonoscopy were started on or received additional treatment for endoscopic recurrence. The primary end point of the POCER study was postoperative endoscopic recurrence at 18 months. The 18-month endoscopic recurrence rate in patients previously undergoing a colonoscopy at 6 months was 49% compared with 67% in those who had not had a 6-month colonoscopy. In a post hoc analysis of the POCER study, the authors observe that the 6-month endoscopic recurrence rate in high-risk patients receiving thiopurine was 45% significantly higher compared with 21% with anti-TNF therapy (13).

To summarize, the treatment accordingly to risk factors can be administrated as follows (15):

Postoperative recurrence risk



Adapted after Regueiro M. Clinical Challenges and complications of IBD

Conclusions:

CD diagnosis is not always easy. In our patients it took more than 5 years to establish a correct diagnostic. Surgery does not cure CD. The risk of postoperative recurrence should be stratified; the best method of assessment – ileocolonoscopy. Drugs that can prevent recurrence are Metronidazole, azathioprine, biological therapy. The problems that remains are when is the proper time to induce therapy, what is the duration of therapy, do we prefer a step up versus top down strategy and can we by medication can change the course of the disease? The new therapies (Vedolizumab, Ustekinumab) already approved in CD wait to find a place in postoperative management of CD patients.

Conflict of Interest

Authors have no conflict of interest to disclose

Ethical issues

The study was approved by the Ethics Commission of the University Hospital "St. Spiridon" Iasi

References

1. Frolkis AD, Lipton DS, Fiest KM, et al. Cumulative incidence of second intestinal resection in Crohn's disease: a systematic review and meta-analysis of population-based studies. *Am J Gastroenterol.* 2014; 109: 1739-1748.

2. Swoger JM, Regueiro M. Evaluation for postoperative recurrence of Crohn disease. *Gastroenterol Clin North Am.* 2012; 41: 303-314.
3. Rungoe C., Langholz E., Andersson M. et al. Changes in medical treatment and surgery rates in inflammatory bowel disease: a nationwide cohort study 1979-2011. *Gut.* 2014; 63: 1607-1616.
4. Herbert Tilg, Geert D'Haens. How to Manage Crohn's Disease After Ileocolonic Resection? *Gastroenterology* 2020;159: 816–820.
5. Renna S., Camma C., Modesto I., et al. Meta-analysis of the placebo rates of clinical relapse and severe endoscopic recurrence in postoperative Crohn's disease. *Gastroenterology.* 2008; 135: 1500-1509.
6. Savarino E, Bodini G, Dulbecco P, et al. Adalimumab is more effective than azathioprine and mesalamine at preventing postoperative recurrence of Crohn's disease: a randomized controlled trial. *Am J Gastroenterol.* 2013 Nov;108(11):1731-42.
7. Erős A, Farkasa N, Hegyia P, et al. Anti-TNFα agents are the best choice in preventing postoperative Crohn's disease: A meta-analysis. *Digestive and Liver Disease* 2019; 51:1086–1095.
8. Yamamoto T. Factors affecting recurrence after surgery for Crohn's disease. *World J Gastroenterol.* 2005;11(26):3971-9.

9. Regueiro M, Schraut W, Baidoo L, Kip KE, Sepulveda AR, Pesci M, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. *Gastroenterology* 2009; 136:441–50.
10. Papamichael K, Archavlis E, Lariou C, Mantzaris GJ. Adalimumab for the prevention and/or treatment of post-operative recurrence of Crohn's disease: a prospective, two-year, single center, pilot study. *J Crohns Colitis* 2012; 6:924.
11. Savarino E, Dulbecco P, Bodini G, et al. Prevention of postoperative recurrence of Crohn's disease by Adalimumab: a case series. *Eur J Gastroenterol Hepatol* 2012; 24:468.
12. Kunitake H, Hodin R, Bordeianou L. Perioperative treatment with infliximab in patients with Crohn's disease and ulcerative colitis is not associated with an increased rate of postoperative complications. *J Gastrointest Surg* 2008; 12(10):1730–1736., discussion 1736-1737.
13. De Cruz P, Kamm M A, Hamilton A L, et al. Crohn's disease management after intestinal resection: a randomised trial. *Lancet* 2015; 385: 1406–17.
14. Regueiro M, Feagan B G, Zou B, et al. Infliximab Reduces Endoscopic, but Not Clinical, Recurrence of Crohn's Disease After Ileocolonic Resection. *Gastroenterology*. 2016 Jun;150(7):1568-1578.
15. Regueiro, M: Clinical Challenges and Complications of IBD.